AstraZeneca

September 11, 2000

SENT UPS NEXT DAY AIR

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852-1448

Re: Draft Guidance
Pediatric Oncology Studies In Response to a Written Request

Reference is made to the Agency's June 15, 2000 draft guidance, "Pediatric Oncology Studies in response to a Written Request." This draft Guidance was distributed for the purpose of obtaining comments and suggestions from the pharmaceutical industry and the public. Further reference is made to the FDA Guidance for Industry "Qualifying for Pediatric Exclusivity (September 1999),"which outlined the standard process by which a sponsor may obtain agreement, in the form of a Written Request, for the voluntary conduct of pediatric studies in exchange for 6-month of market exclusivity.

The purpose of the letter is to provide the Agency with comments on the above-mentioned draft Guidance within the 90 days requested (Ending September 15, 2000). For clarity excerpts from the guidance have been bolded, followed by AstraZeneca comments.

The following recommendations are provided to applicants who receive a Written Request for pediatric studies of oncology drugs:

1. **The FDA would use flexible regulatory approaches, specially in the absence of available therapies to treat refractory stages of pediatric cancers. Approval could be based on provisions under 21CFR314 (Subpart H) and 21CRF601 (SubpartE). Acceptable levels of safety for studies with small number of patients could be justified under 21CRF312 (Subpart E).**

   The wording is vague as to which regulatory approaches will be made flexible. More information or clarity is needed regarding 'flexible regulatory approaches.'

2. **The Written Request will usually be a part of an overall development plan for the drug. A specific disease may be targeted or several studies in various tumor types, typically brain tumors, solid tumors or hematologic tumors.**

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The draft guidance for Pediatric Oncology Studies also mentions that Phase 2 studies should be considered for a range of potential indications. Therefore, clarification is needed on whether this means that in the Written Request several efficacy studies (evaluating different tumor types) would be requested in order to grant exclusivity or whether evaluation of several tumor types results in additional periods of exclusivity.

3. **Phase 3 studies usually will not be requested in a Written Request as a pre-requisite to grant the 6-month pediatric exclusivity**.

Please clarify whether a Phase 3 study will be requested as part of a Phase IV commitment if the drug is approved for the indication studied in the pediatric population. This is not clear in the guidance.

4. **The study protocol should be discussed with a pediatric cooperative study group.**

Clarification is needed on the Agency's rationale for emphasizing the importance of medical/scientific feedback from a cooperative group versus feedback from one or two thought leaders in pediatric oncology. Given the limitations of pediatric cooperative groups, it could be anticipated that those companies successfully establishing partnerships with these groups could lock-up their resources. In addition, it is not clear to what extent this statement imply that the Agency defer part or all of its regulatory review and final determination regarding number/type of studies required, study design, etc., to recommendations provided by the cooperative group.

5. **A typical Written Request for pediatric oncology studies will ask for Phase I and Phase 2 studies. If Phase I studies demonstrate an acceptable level of safety, Phase 2 studies will generally be required. However, if a Phase I study appears to demonstrate unacceptable toxicity, in general, and with FDA agreement, the conditions of the Written Request would be considered as having been met and not further studies would be required. Product labeling information would be updated accordingly.**

Clarification is requested regarding the minimum numbers of studies that could be conducted or whether an accelerated Phase 1 / 2 study could meet the terms of the Written Request. These items are not discussed in the guidance.

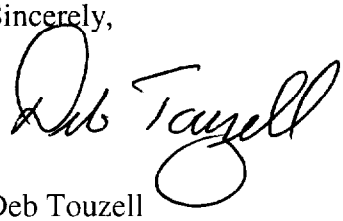
6. **In general, it would be acceptable to use unvalidated surrogate endpoints with a sponsor's commitment for the conduct of additional studies as required by 21CRF 314 and/or 21 CRF 601. Completion of confirmatory studies would not be required prior to pediatric exclusivity determination**

Please clarify whether the Phase 3 study will be a Phase IV commitment if the drug is approved for the indication studied in the pediatric population is not clear in the guidance.

In closing, it is noted that the agency did not address the issue of timings or how the division will review the proposals for written agreements. Clarification or description of this topic would be helpful to a sponsor.

Please do not hesitate to contact me if you have any questions regarding this review.

Sincerely,



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